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Coronavirus Disease 2019 Viremia, Serologies, and Clinical Course in a Case Series of Transplant Recipients

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ABSTRACT

Here we report a single-center cohort of 6 patients (4 kidney only, and 2 simultaneous liver/kidney transplants) diagnosed with COVID-19 at a median of 1.9 years (range = 0.2-9.3 years) post transplant. Five (of 6) patients required inpatient admission, 2 patients (mortality = 33%) died. Among those with mortality, an increased concentration of inflammatory biomarkers (interleukin-6 and C-reactive protein) was noted with a lack of response to interleukin-6 blockade, remdesivir, and/or convalescent plasma. None of the kidney-only transplants (4/6; 67%) had elevation in plasma donor-derived cell-free DNA above the previously published cut-off of 1%, suggesting absence of significant allo-immune injury. Four (of 5) admitted patients had detectable SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2) in blood on samples obtained at/during hospitalization. Of the 4 discharged patients, 2 patients with undetectable virus on repeat nasopharyngeal swabs had seroconversion with positive SARS-CoV-2 IgG formation at 30 to 48 days post infection. One patient had prolonged shedding of virus on nasopharyngeal swab at 28 days post discharge despite lack of symptoms. In this preliminary report, we find that immunocompromised transplant patients had higher rates of RNAemia (67%) than reported in the general population (15%), seeming absence of allo-immune injury despite systemic inflammation, and formation of IgG overtime after recovery from infection.

SEVERE acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, Hubei province of China as the cause of a new viral respiratory illness named coronavirus disease 2019 (COVID-19) [1]. It is clear that risk factors such as old age, chronic kidney disease, diabetes, and hypertension predispose the general population to severe disease [2]. These same risk factors abound in the end stage renal disease and kidney transplant (KT) population. These risk factors along with immunosuppression places KT recipients in a uniquely high-risk category of high mortality from COVID-19.

A number of case series have described the clinical manifestations and high mortality (15%-30%) of COVID-19 in KT recipients [3-5]. There has been a significant decline in kidney transplants all over the world regardless of prevalence of the disease [6]. Studies describing SARS-CoV-2 viremia, serologic responses in immunosuppressed patients, and response to modulation of

immunosuppression are the needed next step. Several unknowns remain. First, it is unclear as to which factors determine the severity of clinical course of disease in immunocompromised patients. Second, it is unknown whether COVID-19 triggers allo-immunity and rejection. It is plausible that the cytokine release syndrome associated with COVID-19 and reduction in immunosuppression may predispose KT patients to rejection [7]. Third, although studies in the general population suggest rapid formation of IgG within a few days of COVID-19 infection, these data are unavailable for immunocompromised KT patients who have a blunted response to both viral infections and vaccines [8,9].

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In this first case series, we report the characteristics, inflammatory immune response, biomarkers of graft injury along with SARS-CoV-2 RNAemia and serologic response in a small cohort of kidney/liver transplant patients.

MATERIALS AND METHODS

Patient Selection

Between March 2020 and May 2020, 6 symptomatic kidney transplant recipients presented to the Virginia Commonwealth University hospital and tested positive for SARS-CoV-2. These adult (age >18 years) solid organ transplant recipients were retrospectively assessed.

Nasopharyngeal Swab Testing

All initial tests to diagnose COVID-19 used qualitative real-time reverse transcriptase PCR (RT-PCR) of nasopharyngeal (NP) swab specimens. The study was approved by the Virginia Commonwealth University Institutional Review Board.

Blood Testing

A commercial real-time fluorescent RT-PCR kit (BGI Genomics Co Ltd, Shenzhen, China) was used to detect RNAemia from plasma samples collected at the time of diagnosis. The kit contains a sequence-specific fluorescent probe that uses 6-carboxyfluorescein as a reporter and an internal reference probe that uses VIC/HEX (2'-chloro-7'-phenyl-1,4-dichloro-6-carboxy-fluorescein/4,7,2',4',5',7'-hexachloro-6-carboxy-fluorescein) as a reporter. The total reaction volume was 30 μ L and was set-up according to the manufacturer's protocol. The reaction procedure was 50°C for 20 minutes, 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 30 seconds. A threshold cycle (*C_t* value) of less than 37 in the 6-carboxyfluorescein channel and less than 35 in the VIC/HEX channel was used to indicate a positive sample.

Initial serologic testing on samples obtained at the time of initial diagnosis was performed using the GenScript cPass SARS-CoV-2 Neutralization Antibody Detection Kit per manufacturer instructions. The cPass kit does not require live biological materials and detects all circulating neutralizing SARS-CoV-2 antibody isotypes (IgG, IgM, IgA, IgE, and IgD) that block the interaction between the receptor binding domain of the viral spike glycoprotein with the angiotensin-converting enzyme 2 cell surface receptor. Subsequent serologic testing for IgG on recovered patients was performed commercially through Viracor-Eurofins Laboratories (Lee's Summit, MO, United States). An IgG titer of >11 units is considered positive and was reported to be positive in 9 (100%) controls tested for validation beyond Day 12 post infection.

dd-cfDNA Measurements

Venous blood was collected in Streck Cell-Free DNA blood collection tubes and shipped to the central Clinical Laboratories Improvements Act certified laboratory at CareDx, Inc. Details of the standardized specimen processing and analytical methods to determine the percentage of dd-cfDNA (AlloSure) have been published [10]. The targeted next-generation sequencing assay employs highly polymorphic single nucleotide polymorphisms to quantify dd-cfDNA without the need for separate genotyping of the recipient or the donor.

RESULTS

Between March 2020 and May 2020, 4 KT recipients (67%) and 2 simultaneous liver kidney transplant (SLKT; 33%) recipients tested positive for COVID-19 PCR by NP swab specimen. The demographics of these patients are presented in Table 1. The median age was 56 years (range: 51-69). Four of 6 (67%) were African American, and the majority of patients had a history of hypertension (6/6; 100%) and diabetes (5/6; 83%). The median time from transplant was 1.9 years (range: 0.21-9.3 years).

Clinical Presentation

All patients presented with the triad of fever, dyspnea, and cough. They were negative for any other viral or bacterial respiratory infections. Only 2 (33%) patients required supplemental oxygen (2-4 L/min) at the time of presentation. Four (67%) patients had infiltrates on chest imaging. Three (50%) patients had diarrhea at the time of presentation. Sequential Organ Failure Assessment (SOFA) score on average at the time of presentation was 2 ± 1.6 . Only one patient presented with acute kidney injury related to prerenal causes from diarrhea for several days before presentation. There were no cases of new onset proteinuria or active urine sediment.

Laboratory biomarkers are presented in Table 2. At presentation none of the patients had leukopenia with a mean absolute neutrophil count of 4600 ± 1982 per mm^3 . The majority of the patients (4/6, 67%) were profoundly lymphopenic (lymphocyte count <1000 per mm^3) and the mean absolute lymphocyte count was 717 ± 474 per mm^3 .

Clinical Course

One patient with fever, cough, and dyspnea but no infiltrate was discharged with reduction of mycophenolate mofetil (MMF) dose by 50% (patient 1). He was seen weekly by telemedicine and improved. Those that remained out of the intensive care unit were discharged in improved condition (3/6; 50%; patients 2, 5, and 6). The 2 patients (33%: patients 3 and 4) who developed hypoxemic respiratory failure required mechanical ventilator, vasopressor, and renal replacement support. Eventually both these patients died. Of the 2 deaths one was the recipient of SLKT, and the

Table 1. Patient Demographics

ID	Age	Sex	Race	Transplant Type	Years from Transplant	Comorbid Conditions	Follow-up (d)
1	56	M	AA	DDKT	2.9	HTN, DM	72
2	57	F	White	SLK	0.9	HTN, DM	16
3	64	F	AA	DDKT	9.3	HTN, DM	11*
4	69	M	White	SLK	0.7	HTN	15*
5	55	M	AA	DDKT	0.2	HTN, DM	26
6	51	M	Hispanic	DDKT	4.7	HTN, DM	55

Abbreviations: AA, African American; DDKT, deceased donor kidney transplant; DM, diabetes mellitus; F, female; HTN, hypertension; M, male; SLKT, simultaneous liver kidney transplant.

*Deceased.

Table 2. Clinical Characteristics (At Presentation)

ID	Hematological Markers			Inflammatory Markers					Serology and Biomarkers					Follow-up dd-cfDNA (%) (With Reduced Immunosuppression)
	ANC (per mm ³)	Lymphocyte Count (per mm ³)	IL-6 (pg/mL)	CRP (mg/dL)	Ferritin (16-150 ng/mL)	Serology (U)			NP Swab Cycle Threshold Value	Blood Cycle Threshold Value	dd-cfDNA (%)	dd-cfDNA (%)		
						NaB	IgG	RNAemia						
1	2600	1500	N/A	N/A	N/A	N/A	Positive	N/A	N/A	N/A	N/A	N/A		
2	1300	200	31.8	2.2	658	Positive	N/A	Negative	23.2	N/A	4.8 [†]	1.2		
3*	5800	500	58.6	22.3	1591	Negative	N/A	Positive	15.8	24.67	0.29	N/A		
4*	6900	600	300	16	1108	Negative	N/A	Positive	13	29.7	6.4 [†]	N/A		
5	5900	300	7.7	2.2	2335	Negative	N/A	Positive [‡]	18.4	30.9	0.41	0.39		
6	5100	1200	23.9	2.0	46	Negative	Positive	Positive	24.9	33.9	0.26	0.33		

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein (0-0.5 mg/dL); dd-cfDNA, donor-derived cell-free DNA; IL-6, interleukin-6 (0-12 pg/mL); N/A, not available; NaB, SARS-CoV-2 neutralization antibody for all Ig isotypes; NP, nasopharyngeal.

*Deceased.

[†]Simultaneous liver kidney.

[‡]Retest.

other was a KT-only recipient with a history of chronic antibody mediated rejection.

Treatment and Immunosuppression Management

All interventions are summarized in Table 3. All patients (83%) admitted to the hospital had their MMF stopped at the time of admission. The only patient managed as an outpatient had MMF reduced by 50%. Two (33%) received remdesivir for treatment, one of whom was discharged in stable condition. Both the patients who were in the intensive care unit, received interleukin-6 (IL-6) blockade and one of those received convalescent plasma.

Biomarkers of Graft Injury and Markers of Inflammatory Response

All KT-only recipients had low-level, donor-derived, cell-free DNA (dd-cfDNA) at the time of presentation (<1%). Initial testing for dd-cfDNA was done before adjustment of immunosuppression. The mean dd-cfDNA in the KT only recipients was 0.32 ± 0.06%. Two patients who underwent subsequent dd-cfDNA testing on reduced immunosuppression within 2 weeks did not show any clinically significant change (0.26% to 0.33% and 0.41% to 0.39%). In SLKT recipients the dd-cfDNA is not validated; however, our main purpose was to establish a baseline that we could follow in order to guide future immunosuppressive management while correlating with allograft function and clinical response to infection. As expected, both these patients had higher average dd-cfDNA of 5.6 ± 0.8% as compared with their KT-only counterparts. They did not show any evidence of biochemical liver dysfunction. Four weeks later while on reduced immunosuppression the surviving SLKT recipient (patient 2) had a decline in dd-cfDNA from 4.8% to 1.2%.

At presentation the markers of inflammatory response, specifically IL-6 (mean: 104 ± 109 pg/mL), C-reactive protein (CRP) (mean: 10.6 ± 8.56 mg/dL), and ferritin (mean: 851 ± 782 ng/mL), were high. The 2 patients who presented with the highest IL-6 and CRP levels (patients 3 and 4; Table 2) showed rapid progression of disease and eventually died.

Virologic Testing

All 5 patients admitted for management underwent qualitative RT-PCR for detection of RNAemia at the time of admission. Four of 5 patients (80%) (patients 3, 4, 5, and 6) had RNAemia, of which 3 had RNAemia (patients 3, 4, and 6) at the time of presentation, and patient 5 was found to have RNAemia on repeat testing 2 weeks after presentation. Patient 2 had no detectable RNAemia at the time of admission.

At the time of presentation, only one patient without evidence of RNAemia (patient 2; Table 2) was positive by the GenScript cPass SARS-CoV-2 Neutralization Antibody test, and the others were negative. This patient had symptoms for 7 days before admission, while the others had a gap of no more than 3 days from symptom onset. The 2 patients

Table 3. Immunosuppression and Management

ID	Induction Agent	Maintenance Immunosuppression	Immunosuppression Change	Treatment			
				HCQ	Remdesivir	IL-6 RA	CP
1	Thymoglobulin	FK/MMF/Prednisone	MMF 1 g to 0.5 g/day	✓			
2	Basiliximab	FK/MMF	MMF held				
3*	Thymoglobulin	Belatacept/MMF/Prednisone	MMF held	✓		✓	✓
4*	Basiliximab	FK/MMF/Prednisone	MMF held	✓	✓	✓	
5	Thymoglobulin	FK/MMF/Prednisone	MMF held		✓		
6	Thymoglobulin	FK/MMF/Prednisone	MMF held	✓			

Abbreviations: CP, convalescent plasma; FK, tacrolimus; HCQ, hydroxychloroquine; IL-6 RA, interleukin-6 receptor antagonist; MMF, mycophenolate mofetil.
*Deceased.

who were more than 30 days post initial infection were retested and negative for the RT-PCR from a NP swab. They underwent repeat serologic testing for SARS-CoV-2 IgG as outpatients on day 31 and 48 post initial presentation. Both had detectable anti-COVID-19 IgG. One surviving patient post discharge continued to have a positive RT-PCR on NP swab for 28 days of follow-up.

RT-PCR Cycle Threshold

The cycle threshold (Ct) for the qualitative RT-PCR testing for the NP swab was further evaluated (Table 2). Ct levels are inversely proportional to the amount of target nucleic acid in the sample.

For NP swabs, the Ct threshold was not available for patient 1, as this was done in a commercial lab; however, for the remaining 5 patients the average Ct value was 19.06 ± 4.45 . The 2 patients (patients 3 and 4) who developed hypoxemic respiratory failure and died had a lower average Ct value of 14.4 ± 1.4 (range: 13-15.8) as compared with those who survived and had an average Ct value of 22.17 ± 2.75 (range: 18.4-24.9).

For blood, the 4 viremic patients had an average Ct value of 29.79 ± 3.33 . The 2 patients (patients 3 and 4) who developed hypoxemic respiratory failure and died had a lower average Ct value of 27.19 ± 2.52 (range: 24.67-29.7) as compared with those who survived had an average Ct value of 32.4 ± 1.5 (range: 30.9-33.9).

DISCUSSION

There are significant knowledge gaps with regards to COVID-19 in KT patients. In this small case series, we confirm several findings from previous publications: higher mortality compared with the general population (2/6; 33%), presence of comorbidities, co-existence of lymphopenia, and the association of inflammatory markers with outcomes. In addition, we present novel findings.

In our case series we found that 80% (4/5) of patients who were tested for SARS-CoV-2 RNA in plasma tested positive for presence of circulating virus. Three of these patients tested positive at the time of presentation, and the fourth tested positive on re-testing 2 weeks later. This may be due to a false negative initial RT-PCR that returned positive on

re-testing. One patient without RNAemia at the time of presentation had evidence of neutralizing antibodies. This patient presented with a longer duration of symptoms, did not undergo lymphocyte depletion induction at the time of transplant, and had been maintained on lower baseline immunosuppression. All factors could have contributed to the lack of RNAemia at the time of presentation.

To date there have been no studies demonstrating RNAemia in solid organ transplant recipients. However, this seems to be a much higher rate of RNAemia when compared with the few studies in the general population where RNAemia rates have been found to be ~15% [11,12]. In fact, in one of our patients with severe disease, detectable virus was present even 2 weeks after presentation. Given the lack of host immunity, this data seems to raise the tantalizing possibility that the presence of SARS-CoV-2 RNA in blood may correlate with clinical diagnosis, hematogenous spread, extra-pulmonary manifestations, and severity of disease. In our evaluation of the Ct values for the NP swabs and blood we found that those with most severe manifestations and death had lower Ct values indicating higher viral particles as compared with those who survived and improved. While ours was a qualitative assessment of RNA in the blood, in the future it will be interesting to further delineate if RNAemia is common and if the quantitative viral load may be of informative value. This is particularly relevant, as NP swabs are both subject to frequent false negatives and pose significant discomfort to patients [13].

One of our patients had evidence of viral shedding even after 28 days despite presence of SARS-CoV-2 IgG. Similar data among KT patients have been reported by other authors [14]. It is unclear if this is an infectious virus, and more studies will be needed to further investigate this given the implications for return to work, clinic environments, and adjustment of immunosuppression.

We also report data on seroconversion in KTs for the first time. Both of our patients who recovered and were at least a month post infection developed SARS-CoV-2 IgG. Both these patients were maintained on reduced-dose MMF until the time of seroconversion after which MMF was increased to the preinfection dose with no short-term ill effects. This is encouraging, as it indicates that an impaired immunity may not prevent antibody formation. Although it is not yet

established if seroconversion confers immunity in the general population [8,9], the low re-infection rates and early reports of favorable efficacy of convalescent plasma in patients with severe COVID-19 manifestations [15–18] suggest that this may be true.

Finally, we present data on markers of graft injury. Acute kidney injury has been reported widely in COVID-19 infected immunocompetent patients. In an interesting autopsy report endothelialitis was reported in a transplant kidney [19]. It is unclear whether this represented allo-immune rejection or thrombotic microangiopathy related to COVID-19. Although we did not see any evidence of systemic thromboembolism, autopsies were not performed on the 2 deceased patients. We do report that despite a robust immunologic response to the virus as measured by inflammatory markers, we found that graft function and dd-cfDNA, a validated biomarker to detect immunologic graft injury remained low at presentation allowing for reduction of immunosuppression. Given the almost universal presence of lymphopenia, elimination of MMF was necessary. In the 2 patients where consecutive dd-cfDNA results were available, we did not observe any significant elevation in dd-cfDNA despite a reduction in immunosuppression. Although the 2 SLK patients had higher average dd-cfDNA of $5.6 \pm 0.8\%$ as compared with their KT counterparts, they did not have any evidence of liver dysfunction. The dd-cfDNA results on the SLK patients remained within the normal range based on the few studies on liver transplants and dd-cfDNA [20,21]. Future larger studies will be required to further establish objective criteria to guide reduction and re-escalation of immunosuppression in KT patients with COVID-19 infections.

There are several limitations to this small single-center case series. The assays used for RT-PCR have not been validated for blood testing and have different sensitivities and specificities. Similarly, the serologic assays have not been approved by the United States Food and Drug Administration. Nevertheless, the results presented here are biologically plausible and lay the groundwork to spur further investigations in this complex disease.

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